Remarks

In the Office Action dated February 3, 2005, claims 1-15 and 17, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-18 remain in this application.

Claims 1-15 were rejected under 35 USC §112, first paragraph as lacking enablement. The office action points out that BMPs can also bind to activin receptors besides the known BMP receptors BMPRII, BMPR Ia and BMPR Ib such as activin type II receptors in connection with BMP type I receptors or activin type I receptors. Applicants respectfully point out that MP52 also binds to activin receptors. This is clear from the article by Massaguè (1998) cited in the office action. GDF5 is a synonym for MP52. Applicants point out page 758, last sentence in the last full paragraph, which states "However, ActR-11 can bind BMPs 2, 4 and 7 and GDF5 in concert with BMP type I receptors..." and figure 3(b) which states "The ligands which bind according to each mode are listed together with the type I and type II receptor combinations that they recognize". It is clear from these statements that MP52 (GDF5) can also bind to ActR-II and ActR-IIB. In figure 3(b), GDF5 (MP52) is listed together with BMP-2 and BMP-7 which bind to the same receptor type I and receptor type II. BMPs can bind both types of receptors cooperatively in contrast to TGF-β and activins which first bind type II and then type I. Thus, GDF5 (MP52) shows the same general mechanism as other BMPs.

Applicants also point out the general scheme in Figure 1 on page 756 of

Massaguè (1998). With the ligand binding, receptor type I is phosphorylated by receptor type II. The phosphorylated receptor type I first phosphorylates a R-Smad and activates the signal transduction. A signal transduction is not possible without receptor type II since receptor type I cannot be phosphorylated and thus a phosphorylation of R-Smad is not possible. MP52 can bind to the same receptor of type II (BMPR II, AcTR-II, AcTR-IIb) like other BMPs and block signal transduction. Even if other BMPs bind to BMPR Ia with a higher affinity than MP52 (GDF5), this is of no use for the signal transduction since BMPR-Ia cannot be phosphorylated by BMPR II or AcTR-II and/or ActR-IIb.

Though MP52 binds to BMPR Ib, in combination with AcTR-II or ActR-IIb it can bind BMPR Ia or AcTR-I, though the latter only weakly. Applicants point out that weak affinities to particular type I receptors compared to other BMPs are insignificant if the type II receptors are already blocked. Thus, the use of a modified MP52 would also inhibit other BMPs. In view of the above discussed underlying mechanism of signal transduction of BMPs, one skilled in the art would indeed expect a modified form of BMP-2 or BMP-4 to be an effective antagonist against other BMPs and applicants request that this rejection be withdrawn.

Claims 1-15 were rejected under 35 USC §112, first paragraph, as lacking an adequate written description. As discussed above, though MP52 binds to BMPR Ib, in combination with AcTR-II or ActR-IIb it can bind BMPR Ia or AcTR-I. As pointed out in applicant's prior response, page 12, lines 6-13 of the present application indicates that the examples show that a mature modified MP52 is not

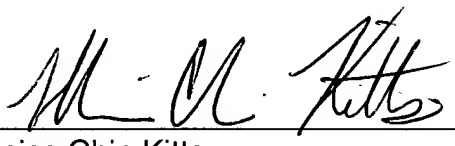
only active as an antagonist against MP52 but also against BMP-2. MP52, BMP-2, BMP-4 and BMP-7 all bind to BMPR-II and thus it was determined that a modified MP52 inhibits signal transduction by BMP-2 proteins. The modified MP52 and modified BMPs would have the same antagonistic activity against other BMPs since they all use the same general mechanism. Applicants contend that the present application provides an adequate written description of modified MP52 and BMP proteins and their antagonistic activity against BMP proteins and request that this rejection be withdrawn.

Claims 12-15 were rejected under 35 USC §112, first paragraph, as lacking enablement. Claims 12-15 have been amended to more clearly indicate that the conditions are related to BMPs. These amendments are supported by page 2 of the present application. In view of these amendments applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 1-18 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By 

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